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Clinical Supplies Manufacture: GMP Considerations

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INTRODUCTION

Applicability of GMP to Clinical Supplies

The Federal Food, Drug, and Cosmetic Act (the Act), Title 21, U.S. Code, section 301 et. seq., establishes that a drug shall be deemed to be adulterated if "...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this article as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." [21 U.S.C. section 351(a)(2)(B)]. This requirement is generally referred to as "CGMP" (current good manufacturing practice), or simply "GMP."

The requirement as written in the law is obviously very broad. It does not define the specific steps manufacturers must take to comply, or the controls that must be in place to ensure compliance. A later section of the Act gives the Secretary of Health and Human Services authority to promulgate regulations for the efficient enforcement of the Act. [In practice, this authority is delegated to the Commissioner of the Food and Drug Administration (FDA).] The FDA, acting in accordance with this authority, has promulgated regulations found in Title 21 of the Code of Federal Regulations (CFR) that sets forth the definitions to be used in specifying GMP requirements for all drugs (21 CFR Part 210) and the procedures and controls necessary for manufacturing of finished pharmaceuticals (human and veterinary), found in 21 CFR Part 211. Part 211 of the regulations is what is generally meant by the term "CGMP" or "GMP" (the acronym GMP will be used in this text). While FDA gives consideration to prevailing practice in regulated industry before specific requirements are written into the regulations as being "*current*, *good practices*," FDA's final basis used to establish GMP requirements is whether the practice is "feasible and valuable" in assuring drug safety, quality, and purity.[1] We also point out that the final GMP regulations are the product of notice and comment rulemaking through publication, first as a proposal in the *Federal Register.* The affected public, including the industry, has an opportunity to comment on the proposed rule before it is finalized.

Because the regulations apply to all "finished pharmaceuticals," and because of the statutory requirement to comply with GMP, there is no question that the regulations apply in a binding manner to the manufacture of clinical supplies. Nevertheless, a debate has existed for many years, and even continues today, regarding exactly how and in what respects a company may differ in its approach to the application of GMP regulations to clinical supplies vs. full-scale commercial production.

BACKGROUND INFORMATION

Clinical supplies, also known as clinical trial materials, are those investigational new drug products intended for administration in human or veterinary (animal) patients during clinical trials.[2] In many respects, there is no difference between the equipment and technology employed to manufacture clinical supplies and that used for commercial production. In other respects, for example, production scale, robustness of the manufacturing process, labeling for clinical trial materials, expiration period (and hence the need for supporting stability data), final container, and even formulation and dosage form, there are important differences that should be taken into account when designing appropriate GMP controls for clinical supplies.

Placebos used in medical treatment to bring about a therapeutic effect without a pharmacologically active ingredient, or placebos used as study controls in clinical trials for new drugs are also subject to the requirements in the current good manufacturing practice regulations (GMP).[3] Because they lack any active ingredient, placebos clearly cannot be tested for potency, but their inactive

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composition can be confirmed. This and other considerations unique to placebos also call for some degree of interpretation of GMP.

Clinical supply manufacturing operations are those areas involved in the manufacture of Phase I–IV clinical trial materials, and may include laboratory (or table-top) scale activities, operations performed in a pilot plant (with batch sizes generally larger than lab scale, but smaller than commercial scale), clinical supplies produced in facilities manufacturing commercially approved products, as well as clinical supplies produced at contract manufacturing sites.[4]

The GMP regulations apply to investigational new drug products produced for clinical trials in humans or animals, whereas those activities earlier in the product development life cycle such as "basic research," discovery or preclinical experimentation are not subject to GMP requirements.

FDA INSPECTIONS OF CLINICAL SUPPLY MANUFACTURERS

Under the Federal Food, Drug, and Cosmetic Act, the FDA has the authority to "...enter, at reasonable times, any...establishment in which food, drugs, devices or cosmetics are manufactured, processed, packed, or held..." [section 704(a), FD&C Act]. This authority clearly includes sites that manufacture or conduct analysis of clinical supplies (for lot release, stability, or in connection with failure investigations). The term "reasonable time" has been interpreted by the courts to mean any time-regulated operations are taking place, regardless of date, day of the week, or time of day or night. Inspections are typically not preannounced, but may be in certain cases.

In practice, FDA only occasionally inspects clinical supply manufacturing sites. However, that should not result in a false sense that an FDA inspection will never take place. Manufacturing sites should always be prepared to undergo FDA inspections. Factors that may cause FDA to inspect clinical supply manufacturers include: Review in connection with a preapproval inspection of the commercial manufacturing site; routine inspections of contract manufacturers who manufacture only clinical supplies; inspections resulting from observed product defects, especially when such defects are linked to adverse reactions in patients (such as contaminated parenterals); in reaction to recalls of clinical supplies; or other factors. The FDA inspections of manufacturing operations for clinical supplies used in Phase III trials are more likely than for operations producing Phase I or Phase II clinical trial material.

Each site should have ready access to a person or persons highly knowledgeable in FDA inspection procedure who can prepare personnel for the inspection and manage it from the company's perspective when it occurs. It is not the purpose of this article to explain in detail how to manage an FDA inspection, but the authors highly recommend that key personnel at each site receive relevant training in preparation for an FDA inspection, and prepare detailed policies and procedures concerning the handling of FDA inspections.

UNDERSTANDING AND USING FDA DOCUMENTS

To properly interpret and apply GMP requirements to a specific context require some research and a good deal of judgment. This process can be greatly aided by reference to a variety of FDA documents in the public domain. Most are available via links found on the FDA website, www.fda.gov. Examples of useful documents include: *Guidelines*; the so-called *Points to Consider* documents issued by the Center for Biologics Evaluation and Research (CBER); *Compliance Policy Guides*; *Inspection Technical Guides*; *Compliance Program Guidance Manuals*; and others.

A key document for interpretation of GMP in a clinical supply setting is FDA's 1991 *Guideline on the Preparation of Investigational New Drug Products* (*Human and Animal*). This Guideline illustrates *when* drug development activities are subject to GMP requirements, the degree of compliance expected at certain stages of drug development, and FDA guidance for several important sections of the GMP regulations.

FDA's position on the applicability of GMP to clinical supplies was clearly articulated in the Preamble to the September 29, 1978 revision of the Drug GMPs (*Federal Register*, Vol. 43, No. 190, 45013–45336) that stated: "GMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages. It is appropriate that the process by which a drug product is manufactured in the development phase be well documented and controlled in order to assure the reproducibility of the product for further testing and for ultimate commercial production."

Compliance Policy Guides are FDA internal documents that provide precedent for GMP (and other) enforcement decisions by FDA's field offices. They are found on the "Field Operations" or "ORA" (Office of Regulatory Affairs) pages on FDA's website under the heading "Compliance References."

Points to Consider documents are topical policy statements by CBER on subjects such as viral inactivation, transgenic animals, and other specialized technology subjects.

Compliance Programs provide FDA investigators with procedural guidance for performing inspections in a wide variety of industries. Some (but not all) of these are also accessible via the ORA link of the FDA's website.

Industry publications and seminars can also provide useful information, but users should be wary of placing too much weight on "podium policy" statements by FDA officials or reading inspection citations issued to other companies. These sources may be misleading when the reader may not know all the facts surrounding any statements.

SELECTED GMP SYSTEMS AS APPLIED TO CLINICAL SUPPLIES

The Quality Organization

21 CFR 211.22 is the regulation that sets forth the responsibilities of the "Quality Control Unit" (QCU). There is no difference in the required roles and responsibilities of the QCU in the manufacture of clinical supplies vs. commercial products. The FDA considers the presence of an adequately staffed and trained QCU, empowered with authority to carry out its responsibility effectively, as a critical factor in GMP compliance.

Companies should be aware that "Quality Control Unit" is a generic term, and the company-specific terminology may differ from the term QCU. For example, in most companies, this unit is referred to as Quality Assurance (QA). Other common terms include Regulatory Compliance, QA/QC, or in some cases, the Regulatory Affairs group fulfills many, if not all, of the listed QCU functions. In very small companies or "virtual" firms, the QCU may be as small as one person, while in large companies the number of QCU employees may be quite large, and the quality organization may have several subdivisions. Thus, the name given to the QCU and its members is not as important as the authority to implement the required roles and responsibilities.

The regulation requires that the QCU be responsible for the following, at a minimum:

- Dispositioning (approval or rejection) of components, containers, closures, in-process materials, packaging, labeling, and finished products.
- Review of production records to assure that no errors have occurred.
- If errors have occurred, they have been fully investigated.
- Approval or rejection of standard operating procedures (SOPs) and specifications.
- Approval or rejection of changes.
- Oversight of contracted manufacturing operations (including testing).
- Approval or rejection of all activities having a potential impact on the safety, purity, potency, quality, and efficacy of the products being manufactured.

The FDA expects (and many other regulatory authorities require) that the QCU will have full independence from other units. This is to provide the maximum degree of assurance that the QCU's decisions will be free of conflicts of interest and other impediments. Normally, the expectation is that the head of the QCU will report to a very senior level person (CEO, President, COO, etc.) of the company, and that there will not be a situation where the head of the QCU reports to manufacturing, marketing, or other similar functions.

The GMP requires that the QCU should have a qualified laboratory. This may be an in-house laboratory that is part of the QCU itself, or it may be an outside contractor or another company site laboratory. Here again, there is an expectation of independence of the laboratory from manufacturing or other units, in order to assure the maximum degree of objectivity in the data that are generated.

Master (and Batch) Production and Control Records

The specific requirements for master production and control records, and batch production and control records outlined in sections 21 CFR 211.186 and 21 CFR 211.188, respectively, also apply to clinical supplies. Despite these requirements, the level and amount of available documentation for early developmental batches will generally be much less when compared to commercial products, until the manufacturing process becomes more fully defined. Batch production and control records for clinical batches produced will have an increased amount of notes, changes, and other information handwritten on them during execution of clinical batches. The amount of this extraneous information usually coincides with the stage of development for the drug product (e.g., early phase production = more notes and changes), and may include the following:

- Notes of any situations arising during production.
- Problems that occurred.

- Modifications made to the formulation, processing step sequence, processing parameters, or equipment set points.

This information that is annotated on executed master production and control records should be evaluated, reviewed and, if necessary, approved, and incorporated utilizing an established change control system.

In many cases, master production and control records used in the production of clinical supplies start out as "batch cards," which are sometimes printed on a heavier stock paper that may be colored (e.g., blue or green), in order to differentiate them as related to R&D production operations, and not commercially manufactured products.

Buildings and Facilities

While buildings and facilities are required to be of suitable size and construction, as well as maintained in a good condition for both approved products and clinical supplies, the level of protection these areas are required to provide is dependent upon the activities taking place inside a respective area. For example, sterile fill operations necessitate, among other things, high-efficiency particulate air (HEPA)-filtered air, temperature and humidity controls, and Class 100 (Class A) environmental conditions.[5] It would be inappropriate to perform aseptic filling operations for even Phase I clinical supplies in a nonenvironmentally controlled laboratory suite under a hood certified to meet Class 100 conditions. As it will be noted later in this article, there is little to no difference in matters of sterility assurance when comparing clinical trial materials to approved products.[6] Similar discretion should also be exercised for operations such as dispensing, mixing, and packaging because FDA expect buildings and facilities used to manufacture clinical supplies are the same as those for commercial products.

Equipment

As with buildings and facilities, equipment must also be of suitable size and construction, as well as suitably located to facilitate its operation, maintenance, and cleaning (21 CFR 211.63). While there is clearly no difference in regulatory requirements for equipment used to manufacture clinical supplies, when compared to commercial manufacturing (e.g., equipment must be maintained and cleaned at appropriate intervals, measurement devices calibrated, qualified, and operating according to written and approved procedures), cleaning is especially important, in as much as many compounds encountered during drug development are of unknown toxicities that pose additional risks.[7] Generally, fully established and validated cleaning procedures will not be in place during Phase I and II clinical supply manufacture. However, the actual cleaning regimen should be robust enough to minimize the potential for contamination or product carry-over. This may be accomplished via visual inspection, or possibly by verification through actual sampling and analytical testing. Finally, 21 CFR Part 211.105 requirements regarding identification of equipment used in the manufacture of clinical trial material can be satisfied with a single sign, or placard, denoting the material in question, the phase of production, and batch number.[8]

Control of Incoming Materials

General requirements related to incoming materials, which include components, drug product containers, and closures, include establishing and following written procedures for the receipt, identification, storage, handling, sampling, testing, and approval (or rejection) of said items (21 CFR 211.80). Research and development organizations will typically have receiving functions and areas that are separate from those used to receive incoming materials for commercial manufacturing operations. The quantities of components, drug product containers and closures, and the containers holding them are generally smaller when compared to the volumes and sizes of incoming materials received by commercial operations.

It is important to note that FDA expects incoming materials used in the manufacture of clinical supplies to be released by the Quality Unit (21 CFR 211.22). Attempts to circumvent the established receiving operation in order to expedite use of these materials should be avoided. Equally important is the requirement to ensure proper storage and segregation of incoming materials, such that quarantined, released, and rejected items are easily identified, and there is some level of separation among them. Different lots or item numbers of similar materials should not be comingled during storage, in order to avoid inadvertent mix-ups with their use in manufacturing (21 CFR 211.80).

Finally, incoming components (e.g., raw materials) used to manufacture clinical supplies must be tested for identity using a specific identity test (if available). Specifications should be established and confirmed for each lot of components, drug product containers, and closures received (21 CFR 211.84 and 21 CFR 211.94), and all other provisions of 21 CFR Part 211, Subpart E, Control of Components and Drug Product Containers and Closures not noted in this section also apply to clinical supply manufacturing operations.

Qualification and Validation Activities

Qualification activities are normally associated with buildings, facilities, utility systems (e.g., water, air handling, Clean-in-place/Steam-in-place (CIP/SIP), and compressed gases) major equipment (including laboratory instrumentation), whereas validation likely is in reference to those confirmatory tasks related to processes and analytical methods. In simplistic terms, validation (and qualification) can be defined as documented evidence that a process, activity, or piece of equipment can consistently meet its predetermined acceptance criteria and quality attributes.[9] This section will be dedicated towards outlining the requirements for validation of manufacturing processes, as the requirements for buildings, facilities and equipment, and the validation of cleaning processes have been discussed in previous sections.

The FDA has indicated that during development, processes are expected be validated, and this should be completed to the "extent possible." Challenges with earlier stages of development include fewer batches from which to establish physicochemical characteristics (including toxicity and potency), processing parameters, and commensurate equipment set points. There is also a greater reliance on in-process monitoring and testing, and final product testing for Phase I, II, and possibly early Phase III clinical supply manufacture. This more intensive monitoring and testing is needed to supplant full process validation, where multiple batches have not been produced under replicated conditions. Once, as FDA puts it, "a growing body of scientific data and documentation" reaches a point, complete validation of the manufacturing process will be required.[8]

While blending times and tablet press parameters may not be fully established for early phase clinical supply manufacturing of solid oral dosages, those variables have a much lower potential to directly affect product safety than sterility, endotoxin contamination, or objectionable types and levels of particulates do for sterile, parenteral clinical supplies.[6] Because clinical supplies can be incompletely characterized, and are usually given to patients already in weakened conditions,[7] those processes and their related validation data necessary to guarantee patient and product safety (e.g., sterilization and aseptic fill) are expected to be in place as early as Phase I clinical supply manufacture.[6, 8]

Production and Process Controls

Written procedures are required to be established and followed for production and process controls as specified in 21 CFR Part 211.100. Because the specific requirements regarding handling of changes, deviations, and equipment identification are addressed in other sections of this article, and all other provisions of Subpart F are required in order to meet CGMP requirements for clinical supplies, this section will focus on the other aspects of Subpart F that provide unique challenges during clinical supply manufacture.

Yield calculations are not only required according to 21 CFR Part 211.103, but they also provide some measure of process, phase, or step consistency when compared on a batch-by-batch basis. This information may prove useful when continuing process development, process optimization, or in the investigation of any process problems encountered during clinical supply production. Actual yields and percentages of theoretical yield also one of many important measures used to evaluate the validation of a manufacturing process.

Time limitations on production may not be fully known or established during early clinical supply development. However, those operations that are time-sensitive such as mixing or blending times, and drying times should be supported by data that are obtained through developmental studies. Arbitrarily assigning time limits without the benefit of any data, or the working knowledge of the operation in question, should be avoided, and can result in costly developmental errors and product delays.

Reprocessing can be defined as the repeating of a defined step or sequence of steps outlined in a master production and control record, in order to achieve a predetermined endpoint. Written procedures should be established and followed for any reprocessing steps or operations that are incorporated into a developed manufacturing process. The effectiveness of any reprocessing activity should be demonstrated through validation studies and should be fully supported by data.

Sterility Assurance

During inspections, FDA places a great deal of emphasis on the following systems they feel most directly will impact the safety and efficacy of sterile products manufactured,[10] namely:

- Sterilization processes for the drug itself, any components, container/closures, product-contact equipment, and surfaces.
- Depyrogenation processes.[11]
- Water systems.
- Air handling systems.
- Environmental monitoring programs.
- Handling of incoming components.
- Packaging and labeling operations.
- Laboratory controls.
- Lyophilization (if applicable).

In general, the above-mentioned, including procedures, systems and, if applicable, validation should be in place for clinical supply manufacturing operations. This would include validation of processes such as sterilization, depyrogenation, and lyophilization; qualification of water and air handling systems; establishing and following procedures for: environmental monitoring programs, handling of incoming components, packaging, and labeling operations; and CGMP compliance for laboratories performing analyses of raw materials, in-process and final product samples, environmental monitoring activities, and testing in support of clinical supply manufacturing. Additionally, those processes or activities that are product-specific (e.g., sterilization, depyrogenation, the manufacturing process for the finished drug product itself, and analytical testing related to raw materials, in-process and final product testing) should be validated to what has been previously noted as the "extent possible." For example, in the case of sterilization processes such as terminal sterilization using moist heat, all of the following validation and process control requirements would be necessary in order to avoid exposing a patient to a risk of nonsterility:

- Equipment that is qualified, maintained, and calibrated.
- Empty chamber heat distribution studies.
- Heat penetration studies that are product and load pattern-specific.
- Challenges with biological indicators.
- Process controls and monitoring typical for steam sterilization (e.g., time, temperature, and pressure).[6]

Similar logic can be applied to sterilization by filtration or depyrogenation by means of dry heat. In these and other cases, there will be little to no difference in the level of compliance necessary when comparing clinical supply manufacturing to that for the manufacturing for commercially approved products.

Change Control

Change control is one of the GMP systems that is applied somewhat differently in clinical supply manufacture than it is in the manufacture of commercial products. Change control does not have a separate and distinct section in the GMP regulations; however, the management of change is referenced or mentioned in several GMP sections [see, for example, 21 CFR 211.100(a) and 211.160(a)].

In commercial manufacturing, the purpose of change control is twofold:

1. Keep validated systems functioning in a validated state.
2. Maintain the accuracy of approved submissions to regulatory agencies (such as NDAs, ANDAs, BLAs, etc.).

In the manufacture of clinical supplies, normally, manufacturing processes are not robust (and therefore not completely validated) until Phase III, sometimes not until the later stages of Phase III. Therefore, the goals of change control in clinical supply manufacture are somewhat different. Those goals should include:

- Assurance that equipment (including computer systems and software), which has been qualified (installation, operational, and performance qualification), is maintained in a qualified state.
- Support systems (such as water for injection, air handling systems, compressed gases, vacuum, clean-in-place systems, and others) are likewise maintained in a qualified state.
- Any significant modification of the Chemistry, Manufacturing, and Controls section of the IND is noted, and, where applicable, the approved submission is supplemented to provide for the change.
- Key changes in the development of formulation, dosage form, manufacturing process, cleaning procedures, and other key operations are identified for the purpose of documenting them as part of the development history.
- When significant numbers of batches are manufactured using replicate processes (usually in late Phase III trials), changes are evaluated in order to determine if process development is complete, and validation should commence.

Laboratory Controls

The majority of 21 CFR 211.160 (laboratory controls) and subsections can be applied in the same manner for clinical supplies as for commercial products. An exception, in many cases, is the time by which analytical methods validation is required. For new chemical entities or significant formulation changes, new analytical methods may need to be developed. As with manufacturing processes, until such methods are robust it is difficult (or impossible) to validate them to the full extent that is expected for commercial products.

The factors normally considered in analytical methods validation include:

- Specificity.
- Sensitivity.
- Linearity.

- Repeatability.
- Robustness.
- Ruggedness.
- Limit of detection.
- Limit of quantitation.

Analytical method validation should track closely to the stages of development of the method itself. However, it is not realistic to expect complete and thorough validation of the method until its development cycle is complete. An exception to this would be a situation where an accepted compendial method is applied to clinical material (such as a dissolution test or release testing of a compendial component). In these cases, companies must be prepared to demonstrate that consistent acceptable results can be obtained when using the compendial method in the company's laboratory (also known as methods verification). The obvious difference is that a compendial method is not a proprietary method, having been developed fully in a collaborative process. Therefore, transfer of a compendial method to a clinical supply context does not differ from a similar transfer to a commercial product.

Methods for the investigation of out-of-specification (OOS) results should be similar to what is required for commercial manufacturing. However, it is recognized that in many cases, specifications may be less exact and methods may still be under development; therefore, it may be considerably more difficult to determine assignable causes for OOS findings related to clinical supplies.

When considering OOS investigation procedures for clinical supplies, manufacturers must keep certain basic principles in mind. Those basic principles include:

- OOS results must not be arbitrarily dismissed simply because they are unexpected and present obstacles to release of materials.
- Consideration must be given as to whether analyst error, equipment malfunction, inappropriate reagents, or some other detectable and assignable cause was the reason for an OOS result.
- Consideration must be given as to whether a detectable process error or nonprocess related (employee) error was the reason for the OOS result.
- There must be a documented rationale for resampling or retesting, including documentation of the reasonableness of the number of retests that are needed to overcome an OOS finding.
- Averaging of results should be avoided when the purpose of the test is to reveal variability in a batch (such as blend uniformity or content uniformity testing) because averaging tends to hide variability.
- If averaging is employed, OOS results must be included along with within-specification findings, unless they may be discarded by an approved statistical outlier test (either approved in the compendia or in the IND).

Training records for analysts should demonstrate that they have the necessary combination of education, training, and experience to perform the specific methods they are assigned to perform.

Stability testing will be guided mainly by the conditions approved in the IND. However, the manner in which the stability program is managed should be similar to that required for commercial products. For example (not an all inclusive list):

- Procedures to ensure that stability samples are correctly collected and are representative of the batch.
- Procedures to ensure that chambers are qualified (temperature mapped) and monitored for environmental parameters.
- Procedures to ensure that test intervals are consistently met.
- Procedures for the development of stability-indicating analytical methods.
- Complete, clear, and accessible records of all testing, including the preservation of raw data.

Deviations and Failure Investigations

As with commercial manufacturing, product or process deviations, or the failure of any clinical batch or any of its components to meet any of its specifications must be handled by approved procedures and thoroughly investigated (21 CFR 211.192). The investigation report should include, among other things:

- Nature of the deviation or failure.
- Date.
- Affected batch or batches.
- Root cause determination.
- Impact analysis.
- Recommended corrective actions.
- Approval by the Quality Unit.

Apart from being product or process-related, deviations can also be procedural in nature, meaning that certain requirements of a specific SOP were not adhered to. Sometimes the terms "unplanned" and "planned" deviations are also used. Unplanned deviations include those events, activities, or actions that are nonintentional. An example of an unplanned deviation could include shutdown of processing equipment during the manufacture

of a batch due to safety concerns. Planned deviation, on the other hand, is a term that is not favorably looked upon by FDA. A conscious decision not to follow written procedures, manufacturing instructions, or other records required under the predicate rule is, at the very least, a CGMP issue. The FDA expects that deviations will be fully and thoroughly documented, including any decisions made and by whom.

In the clinical supply setting, systems and procedures should be established and followed for handling deviations and performing investigations. For deviations, this would also include trending (either according to defined categories such as equipment, process, etc. by product line or other predefined criteria), timely resolution of the issues, and re-evaluation of process or equipment parameters and specifications, procedural requirements, or other items bearing on the quality or purity of the finished drug product. This re-evaluation is especially important during new product development, where less information may be known about the drug product being studied, the method of manufacture, process capabilities, or sensitivities of test methods. In these and other cases, improperly or incorrectly defined product or process attributes could contribute to an artificially high deviation rate, and more importantly, could suggest that additional product development work is needed.

Complaints and Adverse Reactions

Section 211.198 of the GMP regulations sets forth the requirements for reporting and investigating complaints. This section is intended to assure that when a manufacturer is notified of a product defect, a thorough investigation will be performed to determine the cause of the defect, and whether a recall of the product from the marketplace should be initiated. Of course, these activities are all aimed at protection of patients from harm caused by defective products.

When the product in question is intended only for use in clinical trials, the fundamental purpose of the regulation, protection of patients from defective products, must still be of primary concern. However, the quantity of product at risk, and its limited distribution will impact the process of complaint investigation. For example, the generally smaller amount of product involved may make it difficult to identify low-level occurrences of manufacturing defects. The limited and more tightly controlled system of distribution of clinical trial supplies, however, will likely facilitate and limit the recall process should that be deemed necessary.

Complaints of adverse reactions to clinical supplies are typically seen as reportable events that impact the safety or efficacy of the test article. Companies should give consideration to the possibility that an increase in the frequency or severity of adverse reactions may be linked to a manufacturing defect. For example, a product that has been formulated such that it is superpotent in its final form can be expected to produce adverse reactions of greater severity or frequency than if it was properly formulated. Labeling mix-ups can have devastating impact on patients, or, at minimum, may seriously affect the validity of a clinical trial. Therefore, the following elements should be included in the complaint assessment system:

- Complaints of observable (physical) defects should be promptly and thoroughly investigated to determine the root cause of the defect and the probable scope of its occurrence.
- Complaints of unusual or severe adverse reactions, or significant and unexpected increases in the number of adverse reactions (including marked lack of efficacy) should be evaluated to determine whether manufacturing errors may have caused or contributed to the observed effects.
- When a product defect is identified, the evaluation should include a health hazard assessment by a qualified person, usually a physician. The FDA's recall policy regulations contain a suggested rubric for performing a health hazard assessment (see 21 CFR 7.41).
- Product defect complaints and adverse reaction data and trends should be periodically compared to determine if there is any correlation between unexpected numbers, types or severity of adverse reactions, and the number and type of reported product defects.
- As with commercial products, careful records of reported complaints, their investigation and resolution are critical to GMP compliance.

Technology Transfer Plans and Reports

Technology transfer plans and reports are used by a research and development organization in order to document their official "transfer" of a newly developed or recently upgraded product/process from the developmental area and facilities to an operations unit and site, usually located in separate buildings, or at an entirely separate and different manufacturing sites. While the format and content has not been formally prescribed by FDA, companies generally include the following information[12] in these documents:

- Definition of responsibilities for key departments; documentation review, approval, and storage requirements.
- Summary of developmental activities completed.

- Summary of scale-up activities; summary of formulation, synthesis, process, and analytical method changes; establishment of impurity specifications; establishment of critical process parameters; identification of validation plans and activities.
- Definition of component, container/closure, and product attributes.
- Analytical methods development and validation summary.
- Descriptions, specifications, design parameters and requirements of facilities, and major equipment and utility systems.
- Definition of the manufacturing process.
- Stability and expiry dating information.
- Change control.
- Reprocessing.
- Cleaning processes, including methods development and validation of the processes and methods.
- Summary of Regulatory Affairs activities, including regulatory commitments, key data and information to be summarized in regulatory filings.

Data Integrity Considerations

The integrity of GMP data should be a vital part of any company's compliance scheme. The term "data integrity" generally means that the raw (source) data and associated data summaries and reports are truthful, accurate, legible, indelible, complete, and readily accessible. This applies whether the data are in hard copy (paper) form or electronic form. The GMP rules allow for the preservation of data through photocopying or other optical reproduction process (microfilming, optically scanning, etc.); however, original documents should be preserved whenever possible.

The fundamentals of good data recording practices should be observed in clinical supply manufacturing in exactly the same manner as required for commercial materials. Those fundamentals include the following:

- Data, and the identification of those responsible for it, should be recorded contemporaneously, or as close to the time of execution of a step or an observation as is practical. Transfer of data from one form to another should be minimized, and should include one hundred percent verification for accuracy by a second person. This serves to enhance the accuracy of the data.
- Hard copy documents should be recorded in indelible ink. Errors are inevitable, and when they occur, the original entry should be struck out with a single line, initialed and dated, the correct information entered, and a brief explanation of the error should be appended as directed by the document and associated procedures.
- Data should always be recorded on forms designed for the specific purpose. Extraneous notations on loose slips of paper (including post-it notes, scrap paper, paper towels, etc.) should be strictly prohibited in a GMP environment.
- Log books, laboratory notebooks (when used), batch production and control records, qualification and validation protocols and reports, investigations of deviations and failures, and other GMP documentation must be carefully identified, controlled, and archived in a manner that will facilitate its prompt retrieval.
- Electronic records (and electronic signatures, if used) must comply with the provisions of 21 CFR Part 11. It is beyond the scope of this article to explain "Part 11" compliance in total, however, the general principle is to construct and maintain electronic records with the same degree of accuracy and linkage to the originator as is achieved with hard copy documents. Each company choosing to use electronic data capture techniques and electronic signatures must thoroughly understand Part 11 and ensure compliance with this regulation.
- Each company should have a policy that strictly prohibits the deliberate falsification, mutilation, obliteration, or destruction of raw data and associated GMP documentation. Companies must insist on strict adherence to such policies and should take aggressive disciplinary action when lapses are detected. Failure to do so may subject the company and its corporate officers to severe regulatory sanctions, including criminal prosecution under the Federal Food, Drug, and Cosmetic Act, or the general criminal laws of the United States (Title 18, U.S. Code). Even inadvertent (nondeliberate) acts that result in loss of data or records should be prevented, and, if they occur, they should be promptly and thoroughly investigated.
- Establishing and following policies and procedures for good documentation practices, numerical rounding, significant figures, and directed audits to ensure the integrity of data contained in records or other documents prior to submission of applications to FDA).

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